REMARKS

New claims 21 and 22 are supported, among others, by original claim 8.

Election/ Restriction

On pages 2 of the Action, the Office acknowledged applicant's election without traverse of Group I (claims 1, 3 to 7, and 9 to 15).

37 CFR §1.821(f) Statement

On pages 2 and 3, the Office expresses the opinion that applicants' statement of April 10, 2007 that the sequence listing submitted therewith "does not extend beyond the original disclosure" does not comply with 37 CFR §1.821(f). Applicants respectfully submit their belief that this statement is sufficient for sequence listings that are e-filed. For e-filed sequence listings, the Office has reduced the 1.821 requirements to a statement that no new matter was introduced (and a request for entry of the sequence listing). Applicants believe that the statement submitted on April 10, 2007 is therefore sufficient. The USPTO web site states:

> "If a filer submits a sequence listing (under 37 CFR 1.821(c)) as a text file via EFS-Web in response to a requirement under 37 CFR 1.821(g) or (h), the sequence listing text file must be accompanied by a statement that the submission does not include any new matter which goes beyond the disclosure of the application as filed. However, if the sequence listing text file complies with the requirements of 37 CFR 1.824, the filer need not submit (i) any additional copies of the sequence listing pursuant to 37 CFR 1.821(e) nor (ii) the statement described in 37 CFR 1.821(f)." (emphasis added)
>
> (see, http://0-www.uspto.gov.mill1.sjlibrary.org/ebc/portal/efs/legal.htm)

Applicants respectfully submit their belief that the "does not extend beyond the original disclosure" (i.e. does not contain new matter) is sufficient (see also "*USPTO News Update" by Christopher Singer, published in Patently-O, on 11/15/06).* However, to further the prosecution of this case, applicants submit the attached Substitute Sequence Listing Statement that uses verbatim the language used on the USPTO's website.

The Office also expresses the opinion that the instant specification fails to comply with sequence rule 37 CFR §1.821 on pages 4, 6 and 7. The Office in particular expresses the opinion that in addition to sequences with no sequence identifiers, the specification, including the claims, fails to use the proper format for referencing a sequence identifier.

Per preliminary amendment of September 1, 2005, applicants introduced sequence identifiers

on pages 4, 6 and 7 as well as in the claims. Applicants have double checked the specification and did not find that any sequence was left out in this designation.
However, applicants noted that "SEQ ID No." was used at different places in the descriptive portion of the specification and "Seq. ID No." in the claims.
Applicants have amended the specification and claims to replace these designation.

On page 3, the Office notes that one IDS was filed in duplicate. Applicants submit that the second IDS, while citing all references again, was submitted to ensure that the Office obtains copies of the marked references originating from the International Search Report (ISR), since applicants could not ascertain that those had been submitted to the USPTO as part of the international file. Applicants regret any inconvenience caused by their submission format.

On pages 3 and 4, the Office rejected the claims 1, 3 to 7, and 9 to 15 under 35 USC §112, first paragraph as not being enabled.

The Office expressed the opinion there is not enough teaching in the disclosure how to make and use VEGF that is altered at position 109 or 112 without undue experimentation. The Office also expresses the opinion that these modifications have not been shown to have any biological effect.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976) (MPEP §2164.01).

Factors that are used to determine whether experimentation is undue, include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) .

The focus of the examination inquiry is whether everything within the scope of the claim is enabled (see factor (A) above).
The present claims are directed at a vascular endothelial growth factor (VEGF) variant, in which at least one amino acid at positions 109 to 112 is replaced by proline or is deleted.
The claims are not limited by a recited use (compare, In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)). When a claim is not so limited, it is well established that any enabled use that would reasonably correlate with the entire scope of that claim is sufficient (MPEP §2164.01(c)). The "reasonable correlation" was also discussed in *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) and *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (MPEP §2164.08)).
Notably, the claims are not overly broad: four amino acids can be replaced or can be deleted. The specification provides examples for the replacement at two of these four positions and for their specific use, thus providing a meaningful limitation of the claims. Specific examples are provided over a wide range of the breadth of the claim (see factor (G) above).
The Examples teach how to introduce mutations via mismatch oligonucleotides at positions 110 and 111. The person skilled in the art, which is highly skilled in the field of molecular biology, would readily be able to make the appropriate changes to mutate any of the other specified amino acids, namely 109 or 112 to determine their usage (see factor (D) above).
Irrespective of that, how a teaching is set forth, by specific example or broad terminology, is not important. *In re Marzocchi*, 439 F.2d 220, 223-24 169 USPQ 367, 370 (CCPA 1971). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art (compare page 3, lines 2 to 12 of the specification).

On pages 4 and 5, the Office rejected the claims 1, 3 to 7, and 9 to 15 under 35 USC §112, second paragraph as being indefinite.

The Office notes that the claims refer to "a vascular endothelial growth factor variant" having an amino acid sequence, wherein amino acid positions are deleted or replaced. The Office expresses the opinion that there is no antecedent basis for the recited positions because there is no reference to any particular amino acid sequence. The Office also notes that there are a number of different art recognized VEGF molecules. The Office draws the conclusion that therefore the recitation that the claims are directed to a VEGF variant are indefinite because the

meters and bounds of what is encompassed by the claims are unclear. The Office refers to different specific variants recited in the specification.

Applicants have amended the claims to further clarify the antecedent basis for the rejected terms in the claims.

Applicant further notes, that the highest U.S. Patent Court, the CAFC, has repeatedly stated, including as recent as, e.g., June of this year (*Young v. Lumenis*, 06-1455, Fed. Cir., June 27, 2007), that claims are indefinite only when they are "not amenable to construction or are insolubly ambiguous."

Similarly, the Manual of Patent Examining Procedure (MPEP) clarifies that all that is required for a particular phrase to be definite is a reasonable degree of clarity and particularity. The MPEP also emphasizes that the definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by those possessing the ordinary level of skill in the pertinent art at the time the invention was made (MPEP §2173.02). The MPEP refers to *Metabolite Labs.* in which the CAFC stated that only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366 (Fed. Cir. 2004).

Thus, in view of the amendments provided herewith, applicants submit that the present claims readily meet the threshold requirement of clarity and particularity.

As the Office noted the specification provides a number of examples of variants that are encompassed within the present claim. The Office also notes that a number of VEGF molecules are known in the art.

Applicants submit that the person skilled in the art would be readily able to discern that the VEGF variant would require to have the particular amino acids described and that the VEGF variant would include a variety of VEGF's including the splice variants as those recited by the Office.

The Office's observes that the end standing "wherein" clause is unclear. In response, applicants

have amended the claims to delete the wherein clause.

On pages 5 to 6, the Office rejected claims 1, 3 to 7, 9 to 11 and 13 to 15 as anticipated under 35 USC §102(a) as being anticipated by Lauer (FEBS Lett, 531(2):309-13 (10/1/2002)) as also cited in the ISR.

Applicants submit herewith a certified translation of the European application EP02005186.5 to which the present application claims priority. In view of the perfected priority claim to said EP02005186.5, which as filed on 3/8/2002, the rejection is moot.

On pages 6 to 7, the Office rejected claims 1, 3 to 7, 9 to 15 as obvious under 35 USC §103(a) over Lauer (FEBS Lett, 531(2):309-13 (10/1/2002)) in view of U.S. Patent 5,219,739 to Tischer et al.

Applicants respectfully submit that this rejection is moot in view of the certified translation of the priority document submitted herewith.

On pages 7 to 9, the Office rejects claims 1, 3 to 7, 9 to 15 as obvious under 35 USC §103(a) over Keyt at al. (J. Biochem. 271(13): 7788-7795 (1996)) and Lauer et al. (J. Invest. Dermatol. 115:12-18 (2000)) in view of Markert et al. (Protein Engineer. 14(10):791-796 (2001)) and U.S. Pat. No. 5,219,739 to Tischer et al.

The Office acknowledges that neither Keith nor Lauer teach a VEGF variant wherein amino acid positions 110 and/or 111 have been mutated or deleted.

However, the Office expresses the opinion that Markert et al. teach site directed mutagenesis to provide proteolytic resistance to enzymatic degradation and that Tischer et al. teach the amino acid and nucleic acid sequences for $VEGF_{121}$ and $VEGF_{165}$.

The Office draws the conclusion that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a VEGF molecule that was resistant to plasmin cleavage using the methods of Markert et al. and the starting materials of Tisher et al.

Applicants note that Markert et al. studies proteases other than plasmin. The activities and specificities of these proteases differ significantly from plasmin and so do the strategies for

preventing them from performing their activity. Notably, the mutant Ala20Pro is resistant towards proteinase K and subtilisin. However, Ala20Pro is NOT resistant towards elastase. This makes clear that no inferences can be drawn with regard to other proteases, in particular not plasmin. Accordingly, the person skilled in the art would also not have had any reasonable expectation of success.

Also, Markert et al. mutate the P1 position (Ala20) with proline to render the protein resistant towards proteinase K and subtilisin.

Claims 4 and 5, however, require that alanine at position P1' (Ala111) (not P1) is exchanged with proline. Thus, resistance can be unexpectedly achieved by exchanging alanine at position P1' with proline. Markert el al. also emphasizes at different places the importance of the substitution (preferably single mutation (see Conclusion)) with the helix breaker proline to achieve the desired results. In the VEGFs of the present invention, resistance towards plasmin could also be achieved by introducing alanine or glutamine at position P1 (Arg110) (page 10, starting at line 10), both of which are not helix breakers such as proline, further suggesting the difference in the nature of the present invention and that of Markert et al.

Applicants have shown above, that claims 1, 3 to 7 and 9 to 15 and 21 and 22 are enabled, has the required degree of definiteness and is non-obvious over the cited art.

An early notice of allowance is therefore respectfully requested.

A two months extension of time is submitted herewith. The Commissioner is authorized to charge any fee deficiencies and overpayments to deposit account number 50-3135.

Respectfully submitted,

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